ATLANTA AREA MULTIPLE MYELOMA SUPPORT GROUP, INC.

Northside Meeting

November 9, 2019

The notes are long, but so much great information!
The November meeting was redirected to the IMF Regional Community Workshop on November 9. The IMF has more than ten of these informative sessions around the country to educate patients and caregivers about the disease, treatment options, and managing side effects. They believe that an informed patient can work together with their healthcare team for better outcomes.

Kelly Cox, from the IMF headquarters in Los Angeles opened the meeting with an overview of the IMF and all that they do on behalf of patients. Through their global presence, they focus on patients through four pillars: Education, Support, Research, and Advocacy. Education includes free publications in multiple languages, InfoLine for calls and emails, workshops in US and Europe, myeloma.org web site, Myeloma Minute weekly newsletter, and teleconferences on critical topics. Support for patients begins with helping 150 support groups around the country and bringing 100 support group leaders together annually to learn and share ideas. Research is global through the International Myeloma Working Group with over 230 myeloma experts from 36 countries and provides research grants to bring new researchers into the myeloma field. The Advocacy team has three people working at the federal and state level to ensure equal access to life-saving treatments. They also work with veterans and global outreach. The IMF has a special initiative to raise awareness that myeloma occurs in African Americans at twice the rate of Caucasians. See more at www.diversity.myeloma.org

Dr. Craig Cole, from Michigan State University, reviewed the history of myeloma and how far we have come to have the targeted treatments today. The first reported case was in 1844 and treatment included a pint of porter daily! Later that year, the protein in the urine was discovered and it was the first biochemical test for detection of cancer. In 1900, myeloma was recognized as cancer of the plasma cells. Today myeloma is the 2nd most

common blood cancer, 32,000 cases will be diagnosed this year and there are about 125,000 patients in the US. Dr. Cole talked about symptoms and urged all patients to learn their lab results: CBC, CoMP, Beta2 MicroG, LDH, Serum Protein, Immuno-fixation, Serum FreeLight Chain, and Urine Protein. He explained Light Chain Ratio and types of M Protein. He talked about imaging for staging the disease and to quantify the activity of the myeloma. A critical point in staging is to have genomic testing with FISH and GEP. This determines risk factors and guides treatment choices.

Dr. Cole explained the different drug classes and how they work. Immunomodulatory drugs, known as IMiDs, are Thalidomide, Revlimid, and Pomalyst. Most cancers depend on angiogenesis, which grows new blood vessels to feed the hungry tumors. IMiDs inhibit the growth of these blood vessels that feed the myeloma in the bone marrow. They also inhibit the adhesion to the bone marrow stromal cells that feed the myeloma cells. In addition, IMiDs activate the natural killer cells in the immune system to kill the myeloma. The other primary drug class is the proteasome inhibitors (PI): Velcade, Kyprolis, and Ninlaro. The longer the myeloma cells live, they create protein waste within the cells. The proteasome is the garbage disposal for these cells. The PI drugs clog the garbage disposal and the cells die from their own internal waste. Amazing how these drugs work to extend lives!

In closing, Dr. Cole noted that it is important to know:

- How to read your M-protein
- What is your MM risk/stage
- What are your therapy options
- What is your response to treatment
- Know what side effects to expect so you can report them
- Who is on your care team
- Obtain a second opinion and ask about clinical trials

The next speaker was Dr. Craig Hofmeister from Emory Winship. He opened with an analogy of MM as termites eating at the skeleton of a house. We can treat with insecticides (chemotherapy) but cannot cure the vast majority of MM patients because we do not kill the myeloma initiating cells – the Queen of the colony. He noted that the risks for developing myeloma are: obesity, African

American descent, advancing age, and close relative with MM. Myeloma begins with MGUS and can progress to smoldering myeloma (SMM), which may be more like to become active myeloma. Diagnosis begins with bone pain, then a biopsy of the bone marrow reveals the clonal plasma cells. Myeloma is defined by the CRAB criteria: C= calcium elevated, R= renal (kidney) damage, A= anemia, and B= Bone holes. The revised diagnostic criteria are SLiM CRAB: S= sixty percent plasma cells in bone marrow biopsy, Li= Light chain ration > 100, and M= MRI abnormalities (>5 mm) in 2+ sites. The SLiM criteria identifies the risk of SMM becoming active myeloma within 2 years.

Dr. Hofmeister stressed the importance of know the stage of your myeloma at the time of diagnosis. That will indicate how quickly the disease will become resistant to treatment. This also impacts your survival rate. Staging is different in myeloma compared to other cancers. With lung, colon, breast, or prostate cancers, early stage means the cancer is isolated to a small part of an organ and there is a better than 50% chance of cure. In those cancers, higher stage means that the cancer is metastatic and has spread throughout the body and cannot be controlled. Myeloma is in the bone marrow and is usually spread throughout the body. In myeloma, stage 1 means that the disease is easier to treat and control. Stage 3 means that the myeloma is harder to treat and the patient needs to stay on more aggressive treatment and monitor the disease closely. Stage 2 is neither stage 1 or 3 and the treatment outcomes are undetermined. “Stage” and “Risk” are different then “Control”. The disease can be controlled regardless of risk or stage with the new treatments that have improved survival. It is important to be informed about your disease and educated on treatment options. He reviewed the treatment options for newly diagnosed patients and options on relapse. He noted how treatments are adjusted for high risk and unfit patients. Dr. Hofmeister explained how Zometa slows the cells the normally remove bone so that there is a reduced risk of fractures in myeloma patients. He noted that Zometa and Xgeva don’t build new bone, don’t prevent all fractures, and don’t allow patients to heal the lytic lesions. We were reminded of the risks of complications with the jawbones when taking Zometa or Xgeva. The biggest risks factor is pulling a tooth after receiving bone directed drugs.

Dr. Cole spoke during a working lunch about treating relapsed myeloma. He clarified that relapse occurs when the cancer returns after

treatment. Refractory myeloma is when the disease is not responsive during therapy. With new treatment combinations, relapsed or refractory patients can achieve an additional response. The typical course of treatment of myeloma consists of multiple remissions or plateaus of the disease. New drugs and new combinations are allowing longer remission cycles and extending lives. As the patient explores options, clinical trials should be considered after a relapse or two. Conditions that influence the selection of treatment for patients with relapsed/refractory myeloma are:

- Disease related – duration of response to last therapy, CRAB symptoms, speed of relapse
- High-risk relapse – disease outside bone/bone marrow, genetic abnormalities, and secondary mutations.
- Patient related conditions – age, level or activity, neuropathy, blood counts, kidney function, recent blood clots, heart attack, or stroke.
- Regimen-related – number or previous lines of therapy, relapsing while on or off maintenance, previous drug exposure, length of response from transplant.

Treatment decisions should revolve around the patient's preference and conditions. Be sure to communicate your desires for lifestyle goals, symptom control, time and travel required for treatment, and choice of clinical trials. The combination of three drugs vs. two drugs are providing much better results with the new therapies. Maintenance options are extending remissions after relapse.

Dr. Cole talked about immune therapies. Immune therapy has been approved to be included in relapse treatment. There are several clinical trials with new antibody therapies that target myeloma directly. Daratumumab and Elotuzumab are immune therapies that attach to proteins on the surface of myeloma cells and signal the immune system to kill the myeloma cells. Those proteins are expressed on myeloma cells and there is little expression on normal cells, so this reduces side effects from the drug. Antibody drug conjugates (ADC) are a new class of drug that has taken an antibody drug and attached a chemotherapy agent to it. When the antibody drug attaches to the myeloma cell, it deposits the chemo into the myeloma cell to kill it. This is an amazing new therapy that is showing great promise in clinical trials. CAR-T cells are another form of immune therapy that uses the patient's own T-cells to kill myeloma cells. The T-cells are harvested in a process similar to stem

cells and then sent to a lab to be engineered as super soldiers killing myeloma cells. The clinical trials are working to extend the response and reduce toxicities from the CAR-T cells. There are many CAR T-cell trials in MM and we will hear much more from the ASH conference in early December. There is anticipated FDA approval of some of the new therapies in the next couple of years. It is more important now to be an informed and empowered patient with multiple myeloma.

Dr. Hofmeister returned to talk about clinical trials. He acknowledged that the Tuskegee trials were a racist study and should have been stopped years earlier. This resulted in the National Research Act of 1974 which states:

- All persons, no matter how weakened, deserve protection
- All research should maximize benefits and minimize harm
- Research must not exploit those readily available or malleable.

In 1978, Institutional Review Boards (IRB) required the establishment of committees to review each research project. Committees include scientists and non-scientists. Look IRB up on Wiki for more info. Points Dr. Hofmeister made on clinical trials:

- Each time you need treatment, consider a clinical trial
- With a disease that will recur, would you be willing to try something different if we knew that it wasn't going to be worse (and maybe better) than standard treatment?
- Misconception that clinical trials are riskier that approved drugs is corrected by the requirement of the FDA and IRB that treatment on a clinical trial has as good a chance for success as standard treatment.
- Misconception that you will be a "guinea pig" is corrected by the opportunity to use new drugs or old drugs in a new way that may improve results and get closer to a cure.
- Misconception that clinical trials should only be for those with no other options is corrected by the guidance that all patients should consider trials at any stages since drugs are being considered for better outcomes within these stages: newly diagnosed, maintenance, and for relapse.
- Misconceptions that if my doctor doesn't mention clinical trials, then it must not be right for me is corrected with the advice of experts that all patients should consult with a doctor that treats only myeloma. Some of the best

myeloma doctors are at research centers working to advance toward a cure.

- Misconception that all oncologists know how to treat myeloma is corrected by an understanding of the massive amount of research in all cancers and a general oncologist could use a specialist's help in dealing with this rare cancer. At ASH and ASCO there are over 1000 myeloma research projects reported annually.
- Misconception that the trial is more important than the patient is corrected by knowing that this is never the case since all trials are monitored closely for safety. You can stop your participation on a clinical trial at ANY TIME for ANY REASON.
- Misconception that any clinical trial is a good trial is corrected by knowing some clinical trials require too many trips, too many biopsies, and limited eligibility requirements. Read all documents and ask what is required and what is optional.
- Misconception that patients will get a placebo on a trial is corrected by the legal guidance that a trial should provide treatment intended to be at the level of the standard of care. There are usually control and experimental "arms" (groups of patients) within a trial and the control group gets the standard care. Both groups of patients get extensive monitoring and attention.

Clinical trials are a great option for treatment and should be considered in your care plan. Ask lots of questions about the standard of care alternatives, the extra procedures required, expected side effects, and transportation issues.

Charise Gleason then talked about being the "Most Valuable Partner" (MVP) on your health care team. Get in the Game – Knowledge is Power. Understand the different roles of all your providers. Ask questions of the entire team and keep notes on issues. The good news is that there are so many treatment options now, but your preferences and situation need to be addressed. Good communication helps you understand your options so you can participate in the treatment decision.

Both the myeloma and the treatments contribute to how you feel. Know the side effects from the disease and the treatments. Work with your healthcare

team to manage the symptoms properly so you can feel better while staying on treatment for better outcomes. Charise reviewed the side effects of the standard treatments and steroids. She offered guidance on dealing with fatigue, depression, and anxiety. Report any fever of more than 100.4 degrees and work to prevent infections. Patients should know symptoms of blood clots and report them immediately. Other side effects that were discussed: GI symptoms of diarrhea and constipation, kidney function risks, bone damage, peripheral neuropathy, and pain management. Living well with myeloma includes keeping up with your primary care screening, adopting a healthy lifestyle, and being knowledgeable through reputable sources such as the IMF web site and InfoLine at 800-452-CURE(2378).
Submitted by Nancy Bruno

Southside Myeloma Support Group
November 23, 2019

Doris opened the meeting with a moment of silence. There were 25 present. The meeting on December 28 will be a discussion on patient status and planning for 2020.

The speaker for January 2020 for Southside MM Support Group: Topic: The Vital Roles of Clinical Trials in Multiple Myeloma, Christina Chase, NP-C, Nurse Practitioner, Emory Winship Cancer Institute

Nancy Bruno and Deborah Thomas brought the slide booklets from the IMF Regional Community Workshop that was held on November 9. The booklets contained all the slides from the speakers as they explained the history of myeloma diagnosis and treatment as well as the current treatments for newly diagnosed patients and relapsed disease. A detailed overview

of the workshop was provided in the December 2019 newsletter and everyone was urged to re-read those notes. When reading, take time to highlight treatment and terms that are unfamiliar to you. Ask your doctor to increase your understanding of the changes in myeloma tracking and treatment. There is so much news and it is important to stay current for better involvement with your healthcare team and the decisions for your future care.

Nancy reviewed the slides from Dr. Craig Cole and his discussion of Myeloma 101. The diagnosis and staging of myeloma has changed over the years. Now there are key criteria that identify MGUS and Smoldering Myeloma (SMM) with more sensitive testing. The doctors are now better able to predict the odds that a SMM patient will progress to full myeloma. Some indicators predict higher risk of progression to myeloma and these are labeled High Risk SMM or HRSMM. Abnormal chromosomes do not determine high-risk smoldering MM in the way that they determine high-risk myeloma. Protein levels, light chain ratio, and the percentage of plasma cells in the bone marrow measure HRSMM. Many clinical trials are being done to evaluate the outcomes when HRSMM patients are treated before they have fully active myeloma. Some of these are called “cure trials” to determine if myeloma can be eliminated with early treatment. Dr. Cole talked about staging myeloma and that the stage of your disease is only important at the time of first diagnosis. This determines treatment protocols since certain high-risk myeloma must be treated more aggressively. The FISH test is the key determining factor and is performed on the first bone marrow biopsy for the stage of myeloma presented.

Nancy then talked about Immunomodulatory Drugs as presented by Dr. Cole. Cancer cells, including myeloma cells,

are very hungry since they are growing at an excessive rate (kind of like a growing teenager!). Myeloma cells start in the bone marrow and they attach to the bone marrow stromal cells (a key component of the bone marrow) to get food. When the myeloma cells grow in excess and overflow the bone marrow, they hi-jack the osteoclasts and osteoblasts that build bone for feeding and this causes the bone lesions. The other food source for the myeloma cells is called “angiogenesis” which is new blood vessel growth around tumors to bring more food (like growing a feeding tube!). Most malignancies depend on angiogenesis to sustain progression. Tumors produce large amounts of angiogenic growth factors to induce new blood vessel production – Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (bFGF). In 1999, 67 myeloma patients were found to have a significant correlation between disease progression and the extent of bone marrow angiogenesis. A new class of drugs was introduced to treat myeloma: Immunomodulators (IMiDs). Thalidomide was shown to reduce myeloma and extend lives. The IMiDs inhibit VEGF for blood vessel growth, break the link to the stromal cells, and they activate T-cells to kill the myeloma. With the success of Thalidomide, the formula was slightly modified to create Revlimid (Lenalidomide) which nearly eliminated the peripheral neuropathy issues. The third generation IMiD is Pomalyst (Pomalidomide) which was approved in 2013. Iberdomide (CC-220) is the newest in this class and is in early clinical trials.

The other vital drug class in the battle against myeloma is the proteasome inhibitor (PI). The myeloma cells produce waste in the form of proteins. Inside the myeloma cell is a proteasome that is the garbage disposer for this waste. The PI drugs block the discharge of the waste from the myeloma cells. Imagine a cell with a blocked sewer pipe. The waste within the cell continues to build up without discharge and the cell eventually

dies from its own waste. The FDA approved Velcade (Bortezomib) in 2003 for relapsed myeloma patients. The second-generation PI was Kyprolis (Carfilzomib), approved in2012. Ninlaro (Ixazomib) is a new oral PI that was approved in 2015. Oprozomib is an oral next-generation of Carfilzomib that is in development.

As most myeloma patients know, Velcade with Revlimid and Dex works is over 95% of newly diagnosed cases. This treatment is from the two drug classes just discussed and now there are more drug classes. Front line treatment is now moving to a 4-drug combination to dramatically reduce myeloma and provide longer remissions. The conclusions from Dr. Cole:

- There have been dramatic improvements in diagnosis and treatment for MM over recent decades. Stay informed!
- Be frank and open when you talk with your nurse and doctor so they can give you the best possible advice and help you manage your disease.
- Know your disease – labs, stage, risk, protein levels, and bone images.
- Actively participate in your care: know treatment options; get second opinions; consider clinical trials; and ask questions!
- Be an informed and empowered patient!

Deborah talked about clinical trials. She urged patients to ask questions about clinical trials and understand the phases. Phase I trials should be a critical option if you fail therapy and nothing is working. Phase I trial may make a difference and will definitely help others. Phase II involves a drug that worked well in Phase I to provide a better chance of survival and distributes it to more participants. Phase III takes

the Phase II drug to a much broader set of patients and compares to the current standard of care. Deborah stressed that patients will not get just a placebo if they have cancer. The laws do not allow that to happen. Patients will get the current standard of care or the new drug. Patients can stop their clinical trials at any time. If the drug is working well for a patient, then they are allowed to continue on that drug for several years.

Dr. Hofmeister talked about clinical trials at the workshop. He acknowledged that Tuskegee was a racist study from start to finish. Ethical principles and guidelines have been established for the protection of human subjects in research. The National Research Act of 1974 protects people in trials and researchers must not exploit those persons available. It also noted that research should maximize benefits and minimize harm. In 1978, Institutional Review Boards (IRB) were required at each institution that supports clinical trials. Each IRB must register with the Office for Human Research Protections (OHRP), and the institution is also required to obtain and maintain a Federal-wide Assurance or FWA, before undertaking federally funded human research. This is an agreement in which the institution commits to abiding by the regulations governing human research. The regulations set out the board's membership and composition requirements, with provisions for diversity in experience, expertise, and institutional affiliation. For example, the minimum number of members is five, at least one scientist,

and at least one non-scientist. The guidance strongly suggests that the IRB contain both men and women, but there is no regulatory requirement for gender balance in the IRB's membership. Dr. Hofmeister corrected many misconceptions about clinical trials. Please see the newsletter from last month for details. Those notes are worth reviewing.

Deborah closed the discussion with a valuable quote:
“The help we seek is in our own hands.”

Submitted by Nancy B.